DETAILED ACTION

The Amendment filed October 13, 2009 in response to the Office Action of May 12, 2009 is acknowledged and has been entered. Claims 94-111, 133 and 136-141 are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 94-111, 133 and 138-141 under 35 U.S.C. 103(a) as being unpatentable over Smit I et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) in view of Smit II et al. (Electrophoresis, 1994, Vol. 15, p. 251-254) **is maintained.**

Rejection of Claim 136 under 35 U.S.C. 103(a) as being unpatentable over Smit I et al. (Biochemical and Biophysical research communications, 1992, Vol. 187. in IDS of November 14, 2007) in view of Smit II et al. (Electrophoresis, 1994, Vol. 15, p. 251-254) as applied to 94 and 108 and further in view of and Builder et al (US Patent 4,511,502) **is maintained.**

Applicant's arguments have been fully considered but fail to persuade. Applicant argues that Smit II does not provide or suggest evidence of position specific modification in which a molecule's catalytic activity is modified without distortion of the binding center of the IL-3 receptor. Applicant's argue that Smith's discussion of IL-3 modification for the study and

localization of zinc binding does not provide or suggest evidence of position specific modification in which a molecule's catalytic activity is modified without distortion of the binding center of the IL-3 receptor. Applicant argues that pending independent claim 110 includes the following limitation: "wherein the human interleukin 3 is modified only at one or more of the following residues: Ala1, His26, Lys2s, Lys66, His95, His9s, Lys100, or Lys116." and that neither Smit I nor Smit II teach any modification of His residues. Moreover, neither Smit I nor Smit II teaches position specific Lys modifications.

In response, the Examiner respectfully disagrees with Applicant's contention. The Examiner notes that Smit I expressly teaches that zinc binding is restricted at Lysine at positions 28 and 100 (see abstract). Smit I teaches that Histidine at position 95 and 98 are involved in zinc binding (see page 865). Smit I further teaches modifying the zinc binding residues in IL-3 and studying the structure function analysis of IL-3 zinc binding residues comprising chemical modifications of human IL-3, monitoring the modification reaction and assaying the biological activity of the modified IL-3. Thus Smit I teaches and suggests specific amino acid position modifications. Examiner agrees that Smit I describes acylation and not alkylation with acetic anhydride. However, because the claims require treating the sample with the acetic anhydride and Smit discloses treating the sample with acetic anhydride, Smit I meets the limitation of present claim 105.

Applicant argues that one of ordinary skill in the art would not be motivated to assay the biological activity of the chemically modified IL-3 because in Smit I, the IL-3 modification was used to study and localize zinc binding and in Smit II, the IL-3 modification was used to study an electrophoresis protocol. Applicant argues that modification of cytokines can also be used to

investigate the spatial structure of cytokines (e.g., chemical cross-linking) and accessibility of residues from the environment. Modification has also been used in the art to find epitopes of antibodies. Indeed, numerous other applications can be contemplated for the modification of cytokines which have no bearing on biological activity.

In response, it is the Examiner's position that Smit I and II expressly teach assaying the biological activity of the modified human IL-3, as discussed in the rejection of record and therefore meet the limitations of the present claims.

Specifically in regard to claim 107, Applicant argues that neither Smit I nor Smit II teach or suggest modification of Histidine residues. In response the Examiner respectfully disagrees. As discussed above Smit I expressly teaches that Histidine at position 95 and 98 are involved in zinc binding (see page 865). Smit I further teaches modifying the zinc binding residues in IL-3.

Specifically in regard to claim 139, Applicant argues that Examiner's assumption about the properties to inhibit native IL-3 is incorrect for the following reasons: "First, Smit I discloses treatment with Endo Lys-C, which results in a peptide consisting of 11-28 S-S 80-100. (Smit I at Figure 4, page 864.) This peptide still has zinc-binding capacity. Second, Smit I discloses treatment with Carboxypeptidase Y to generate peptides by degradation from the C-terminus. (Smit I at page 862.) in the pending application, it was demonstrated that Lys116 is important for biological activity. (Publication of pending application at ¶¶ [0127]-[0128].) The Klein et al. reference (J. Biol. Chem., 272(36): 22630 (1997)) shows that Glu-43 and Lys116 form an important part of the receptor binding site of IL-3. The zinc binding fragment 11-28 S-S 80-100 still has zinc binding capacity. Therefore, any species obtained with Carboxypeptidase Y would first remove the Lys116 (receptor binding) before getting to the zinc binding area. Therefore,

Carboxypeptidase Y treatment would indicate that there is no possibility to selectively remove zinc binding. This suggests that receptor binding is more likely to be harmed than zinc binding and therefore provides a compelling showing that it is not likely that antagonistic activity can be expected after modification according to Smit I. Smit II does not concern either receptor binding or zinc binding. This clearly demonstrates that one of ordinary skill in the art would not expect that the Carboxypeptidase Y-modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by claim 139. Additionally, the zinc binding fragment 11-28 S-S 80-100 can be generated with complete Endo Lys-C and still have zinc binding capacity. This Endo Lys-C fragment contains neither Asp43 nor Lys116. Thus, the Endo Lys-C treatment would indicate that modification of the receptor binding site is considerably more likely than the likelihood of selective modification of the zinc binding site without harming the receptor site. This demonstrates that one of ordinary skill would not expect that the Endo Lys-C modified IL-3 disclosed by Smit I would have the properties to inhibit native IL-3 as required by claim 139.

In response, the Examiner notes that the functional language recited in claim 139 is not considered limiting because the limitation is not part of an active method step of the present invention.

In regard to claim 136, Applicant argues that neither Smit I nor Smit II teach using urea or EDTA. Applicant notes that the only modification in Smit I involves modification with proteases. Applicant respectfully submits that it is not obvious to use protease modification in combination with substances which prevent protease action. Such a combination would be non-sensical because protease modification of Smit I would be impaired by urea and EDTA. Applicant argues that it would not be obvious to introduce substances which prevent protease

action, degradation, or solubility problems. Applicant submits that use of urea and EDTA was not obvious over either Smit I or Smit II because one of ordinary skill in the art would have no motivation to inhibit protease in a method directed to protease treatment (Smit I), nor would it be obvious to modify the method of Smit II when there is no teaching or suggestion of solubility or degradation problems.

In response the Examiner notes that Applicant traversed the above rejection over the combination of the cited references by traversing the Smit I and II references alone. It is noted that the rejection also includes a reference by Builder, who teaches using EDTA as chelating agent to prevent protease degradation and precipitation of the protein. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.1986).

Although Builder teaches using EDTA for a purpose different than it is intended in the claimed invention, adding EDTA in the method of Smit I and II would still be obvious since Builder has recognized the advantages of using the EDTA in protein expression, as discussed on the record.

Thus, because references by Smit I, Smit II and Builder in combination teach the claimed invention as discussed above and on the record, the rejection is maintained.

Double Patenting

Rejection of Claims 94-111, 133 and 136-141 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 54-68 of copending Application No. 11/979,278 **is withdrawn** in view of Applicant's arguments.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on 9:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/

Examiner, Art Unit 1648

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643